

### **REMARKS**

Upon entry of this paper, claims 1-7 and 11 are pending in this application for further examination on merits, while claims 8-10 have been withdrawn.

Claims 1-7 have been amended in this paper for clarification. Support for the amendments can be found in the claims as originally presented. In addition, the amendment to claim 7 can be found throughout Applicants' specification, such as, lines 12-15 at page 2 and lines 6-8 at page 17 of the application as originally filed.

Claim 11 is new. Support for the claim can be found throughout Applicants' specification, such as, lines 13-14, and 27-28 at page 1, and lines 18-23 at page 9 of the original application.

No new matter has been introduced by virtue of the within amendments.

Applicants respectfully reserve the right to pursue any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

Reconsideration and withdrawal of the objections and the rejections of the present application in view of the remarks herewith, is respectfully requested, as the application is in condition for allowance.

### **CLAIM OBJECTIONS**

Claims 4-6 have been objected to under 37 C.F.R. 1.75(c) as allegedly being in an improper claim form. Applicants submit that these objections have been overcome in view of the within claims amendments.

Accordingly, reconsideration and then withdrawal of the objections to claims 4-6 is respectfully requested.

### **CLAIM REJECTIONS UNDER 35 U.S.C. § 112**

Claims 1-7 have been rejected under 35 USC § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse.

Nonetheless, without conceding to the Examiner's allegation and solely for the purpose to facilitate the prosecution of this application, the instant claims have been amended in this paper

for further clarification. Applicants submit that the rejections have now been overcome in view of the claim amendments as presented herein.

Thus, reconsideration and then withdrawal of the rejections under 35 U.S.C. § 112, second paragraph of claims 1-7 is respectfully requested.

### **CLAIM REJECTIONS UNDER 35 U.S.C. § 102**

Claim 7 has been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Schuhmacher *et al.* (Journal of Pharmaceutical Sciences, Vol. 89, No. 8, August 2000, pp. 1008-1121; hereinafter “Schuhmacher”). Applicants respectfully traverse.

Nonetheless, without conceding to the Examiner’s allegation and solely for the purpose to expedite the prosecution of this application, claim 7 has been amended in this paper for further clarification. Specifically, claim 7 as amended now recites a method to determine the relative free fraction of a substance, in which the membrane affinity of the substance in plasma ( $MA_{\text{plasma}}$ ) of the first species and that in plasma of the second species are measured in an erythrocyte-free environment. In contrast, Schuhmacher discloses a method of determining the relative free fraction of a substance, in which the partition is determined using “plasma from various species but only uses erythrocytes from a single species” (*see*, e.g., paragraph 3 of column 2 at page 1009 of Schuhmacher). Thus, Applicants submit that Schuhmacher does not and cannot anticipate the subject matter of claim 7 as amended.

Accordingly, reconsideration and then withdrawal of the rejection of claim 7 under 35 USC § 102(b) is respectfully requested.

### **CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)**

Claims 1-4 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Veronese *et al.* (Br. J. Clin. Pharmac (1988), 26, 721-731; hereinafter “Veronese”) in view of Loidl-Stahlhofen *et al.* (Journal of Pharmaceutical Sciences, Vol. 90, No. 5, May 2001, pp. 599-606; hereinafter “Loidl-Stahlhofen ”). Applicants respectfully traverse.

To properly determine a *prima facie* case of obviousness, the Examiner “must step backward in time and into the shoes worn by the hypothetical ‘person of ordinary skill in the art’ when the invention was unknown and just before it was made.” M.P.E.P § 2142. Three criteria may be helpful in determining whether claimed subject matter is obvious under 103(a): first, if

there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007). With regard to the first criterion, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.3d 690 (Fed. Cir. 1990). “Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious.” *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002). The issue is whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

Claim 1 of the instant application is directed to a method for determining the free fraction of a substance, wherein the method includes the following steps: (a) incubating the substance with a suspension of particles having a lipophilic surface in a protein-free aqueous medium, wherein both the particles and the medium are erythrocyte-free; (b) determining the distribution of the substance between the particles and the protein-free medium; (c) incubating the substance with a suspension of particles having a lipophilic surface in a protein-containing aqueous medium, wherein both the particles and the medium are erythrocyte-free; (d) determining the distribution of the substance between the particles and the protein-containing aqueous medium; and, (e) determining the free fraction of the substance from the distributions determined under steps (b) and (d).

In contrast, Veronese teaches determining the plasma protein binding of a substance through a measurement by erythrocyte partitioning, in which a substance is incubated with erythrocytes in a buffer and then in plasma (*see*, e.g., Abstract and page 723 of Veronese). In detail, the free fraction ( $f_u$ ) of the substance in Veronese is measured as the ratio between the partition coefficients for the erythrocytes/plasma distribution (E/P) and for the erythrocytes/buffer distribution (E/B) (that is,  $f_u = \frac{E/P}{E/B}$ ) (*see*, e.g., column 2 at page 723 of Veronese).

Applicants submit that the free fraction ( $f_u$ ) taught in Veronese is different from that of this invention, as the free fraction ( $f_u$ ) in Veronese is determined between the substance's erythrocytes/plasma distribution (E/P) and its erythrocytes/buffer distribution (E/B), while the substance's partition coefficients in this application are both measured in the erythrocyte-free systems. Indeed, the free fraction ( $f_u$ ) determined in this application has nothing to do with the substance's distribution in erythrocytes. Applying the equation in Veronese, one example of the

free fraction ( $f_u$ ) measured in this application would be  $f_u = \frac{(\text{Non-E})/P}{(\text{Non-E})/B}$  vs.  $f_u = \frac{E/P}{E/B}$  in Veronese, if the substance is partitioned between particles/plasma in step (a) and then between particles/buffer in step (c). Clearly, the present application teaches a fundamentally different way on determining the free fraction from Veronese, which only cares about the substance's partition in an erythrocytes-containing system. Thus, a skilled artisan would agree that Veronese focuses on measuring a different parameter of the substance compared to this invention. Accordingly, Applicants submit that the method disclosed in Veronese for determining the free fraction differs in each and all the steps from the presently claimed method (as all the steps in this invention require that the system/environment is erythrocyte-free). Thus, Applicants submit that Veronese fails in teaching or suggesting the present invention.

Applicants contend that the addition of Loidl-Stahlhofen fails in curing any deficiencies of Veronese. Applicant note that Loidl-Stahlhofen does not even teach a method for determining the free fraction of a substance, let alone such a method performed through the specific steps as required in this invention. Instead, Loidl-Stahlhofen only discloses a method of determining a substance's membrane affinity, which is a completely different parameter of the substance; thus, as well appreciated in the art, "the determination of which is very different from a method of determining the free fraction (*see*, e.g., lines 29-30 at page 2 of the original application).

Further, Applicants note that the *membrane affinity* of a substance as assessed in Loidl-Stahlhofen is determined through quantification of lipid-water partitioning (*see*, e.g., Abstract and column 2 at page 601 of Loidl-Stahlhofen). Although Loidl-Stahlhofen teaches the use of solid-supported lipid membranes, Loidl-Stahlhofen does not teach or suggest incubating the substance with a suspension of particles in any protein-medium (e.g., plasma), let alone measuring the substance's *free fraction* by determining the substance's partition coefficients in a particles/protein environment and in a particles/protein-free environment. As would be agreed by a skilled artisan, Applicants submit that the presently claimed method is patentably distinct from that disclosed in Loidl-Stahlhofen.

Applicants further contend that neither Veronese nor Loidl-Stahlhofen presents any motivation or suggestion for a combination or modification on the methods disclosed therein, let alone a modification that would lead to the presently claimed method. Nothing in either Veronese or Loidl-Stahlhofen suggests that the material/method used in any erythrocyte-containing system would also work for an erythrocyte-free environment (as required in this invention). Further,

unlike Veronese and/or the present invention, Loidl-Stahlhofen measures a distinct parameter of the substance (that is, the membrane affinity vs. the free fraction). Indeed, it is hard to image that anyone skilled in the art would even attempt to combine the teachings in Veronese and Loidl-Stahlhofen, as they differ fundamentally in their purposes and detailed methods for carrying out such purposes. Particularly, a skilled artisan would appreciate the method for determining the free fraction (as disclosed in Veronese) as significantly different from the method for determining the membrane affinity (as disclosed in Loidl-Stahlhofen). Further, while Veronese focuses on determining the *plasma protein binding* of a substance through a measurement by erythrocytes partitioning, Loidl-Stahlhofen does not show any interest in the assessment of a substance's partition in a system other than *lipid-water*. Thus, Applicants submit that a skilled artisan would not be motivated to combine Veronese and Loidl-Stahlhofen, let alone with any reasonable expectation of success to arrive at the presently claimed subject matter.

Even assuming, *arguendo*, that one were to make such a combination, one would still fail in achieving the presently claimed method, since the combination of Veronese and Loidl-Stahlhofen fails in teaching each and every element of the present invention (e.g., incubating the substance with a suspension of particles in a protein-containing aqueous medium).

Further, Applicants submit that the present invention has overcome the disadvantages associated with the existing methods in the art and demonstrated unexpectedly superior results. Specifically, by replacing the existing *erythrocyte partitioning methods* (as disclosed in Veronese) for determining the free fraction, the present invention has dramatically simplified the steps in such methods by adopting *erythrocyte-free environment*, and thus significantly improved the efficiency and accuracy of one's work (*see*, e.g., lines 7-15 and 20-27 at page 2 of Applicants' application). Thus, a skilled artisan would appreciate the method of this invention as particularly suitable for high throughput experiments. Applicants contend that a skilled artisan would not possibly and reasonably predict the above-discussed technical results achieved by the present invention, simply based on the disclosures of Veronese and Loidl-Stahlhofen.

Therefore, Applicants respectfully submit that: first, Veronese, either alone or in combination with Loidl-Stahlhofen, fails in disclosing each and every element of the present invention; second, one of ordinary skill would not be motivated to combine Veronese and Loidl-Stahlhofen, at least due to the facts that their methods are used for distinct purposes and have been conducted in distinct mediums; third, there is no suggestion or motivation furnished by Veronese and/or Loidl-Stahlhofen for a modification on the methods disclosed therein for arriving at the

present invention; and fourth, based on the disclosures of Veronese and Loidl-Stahlhofen, there would be no reasonable expectation in the art to achieve the unexpected advantages demonstrated by the present invention. Accordingly, Applicant respectfully submits that the present invention as recited in claims 1-4 is indeed patentable over Veronese and Loidl-Stahlhofen.

Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) of claims 1-4 over Veronese and Loidl-Stahlhofen is respectfully requested.

Claim 5 has been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Veronese in view of Loidl-Stahlhofen and further in view of U.S. Patent No. 6,977,305 to Leung *et al.* (hereinafter “Leung”). Applicants respectfully traverse.

Applicants submit that the afore-mentioned reasoning rebutting the rejection over Veronese and Loidl-Stahlhofen is applicable in addressing the instant rejection, as the method for determining the free fraction as recited in claim 1 is patentable over Veronese in view of Loidl-Stahlhofen.

Applicant submits that the addition of Leung would not render the subject matter of claim 5 obvious. Leung only additionally discloses using a microwell plate in a high-throughput screening. Indeed, Leung does not teach or suggest any method for determination on the free fraction of a substance. Specifically, Leung does not disclose a method, in which the substance is incubated with a suspension of particles in a protein-free aqueous medium and then in a protein-containing medium, wherein all the mediums are *erythrocyte-free*. Clearly, Leung has not even come close to the subject of making an assessment of the substance based on its distribution coefficients between the particles/protein-free medium and the particles/protein-containing medium (as this application does).

Further, Applicants note that Leung does not furnish any suggestion or motivation which is lacked in Veronese and Loidl-Stahlhofen.

As such, Applicants submit that the method recited in claim 5 is clearly patentable over a combination of Veronese, Loidl-Stahlhofen and Leung. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) of claim 5 is hereby respectfully requested.

Claim 6 has been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Veronese in view of Loidl-Stahlhofen and further in view of U.S. Patent No. 5,411,730 to Kirpotin *et al.* (hereinafter “Kirpotin”). Applicants respectfully traverse.

Applicants submit that the afore-mentioned reasoning rebutting the rejections over Veronese and Loidl-Stahlhofen is also applicable in addressing the instant rejection, as the instantly claimed method is patentable over Veronese in view of Loidl-Stahlhofen.

Applicants submit that a combination of Veronese, Loidl-Stahlhofen and Kirpotin fails to support the obviousness rejection of claim 6. Kirpotin only additionally discloses that lipid particles having a ferromagnetic core are used in studies of the membrane affinity of a drug. Kirpotin does not teach or suggest a method of determining the free fraction of the substance, let alone the specific steps recited incorporated in the instant claim for determining the free fraction. Thus, Applicants submit that a combination of Veronese, Loidl-Stahlhofen and Kirpotin still fails in disclosing each and every element of the presently claimed subject matter.

Applicants note that Kirpotin does not provide any suggestion or motivation to a skilled artisan for modifying its method, let alone a specific modification that leads to the presently claimed method. Accordingly, Applicants submit that the method recited in claim 6 is patentable over a combination of Veronese, Loidl-Stahlhofen and Kirpotin. .

Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) of claim 6 is hereby respectfully requested.

**CONCLUSIONS**

In view of the above, each of the presently pending claims in this application is believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. Should any of the claims not be found to be in condition for allowance, the Examiner is requested to call Applicant's undersigned representative to discuss the application. Applicant thanks the Examiner in advance for this courtesy.

The Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 83901(303989).

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Customer No. 21874

Respectfully submitted,

Electronic signature: /Weiyang Yang/  
Weiyang Yang  
Registration No.: 61,637  
Edwards Angell Palmer & Dodge LLP  
P.O. Box 55874  
Boston, Massachusetts 02205  
(617) 239-0416  
Attorneys/Agents For Applicant